

Role Of Trastuzumab in HER2+ Breast Cancer. Importance of Combined Therapy

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Introduction

The human epidermal growth factor receptor 2 (HER2) is a transmembrane tyrosine kinase that is overexpressed in approximately 20% of invasive breast cancers, due to HER2 gene amplification. This amplification has been associated with more aggressive disease progression and a poorer prognosis. For twenty years, treatment with Trastuzumab has led to an improved outcome and prolonged survival, being established as standard of care in both the adjuvant and metastatic settings.

Despite the clinical benefit, both de novo and acquired clinical resistance have been increasingly recognized among treated patients. About 15% of the patients in early stages of the disease, and 85% in the metastatic settings, relapse after Trastuzumab treatment. However, the elucidation of the mechanisms of de novo and acquired resistance to Trastuzumab, and a better understanding of the intracellular pathways derived from HER2 dimerization, has lead to the identification of potential predictors of response to HER2-targeted agents and the development of novel therapies against HER2 receptor, its coreceptors and their intracellular pathways.

The aim of this review is to study the mechanisms of action of Trastuzumab and discuss the several proposed mechanisms of Trastuzumab resistance and potential ways to overcome them.

Materials & Methods

This scientific review has been made consulting books and articles found in PubMed, Sciencedirect databases and Scopus. The selections were made considering their Abstract, Conclusions, Date of Publication and Journal Impact Factor. Approximately 46 publications have been read.

Main areas of research: HER2+ Breast Cancer, Trastuzumab , Mechanisms of Action of Trastuzumab, Mechanisms of Trastuzumab resistance, p95HER2, Novel targeted therapies for HER2+, Breast Cancer, Pertuzumab, Lapatinib and T-DM1.

I also interviewed the Director of the Molecular Biology Laboratory of the Vall d'Hebron Hospital: **Professor Javier Hernández-Losa**

Results

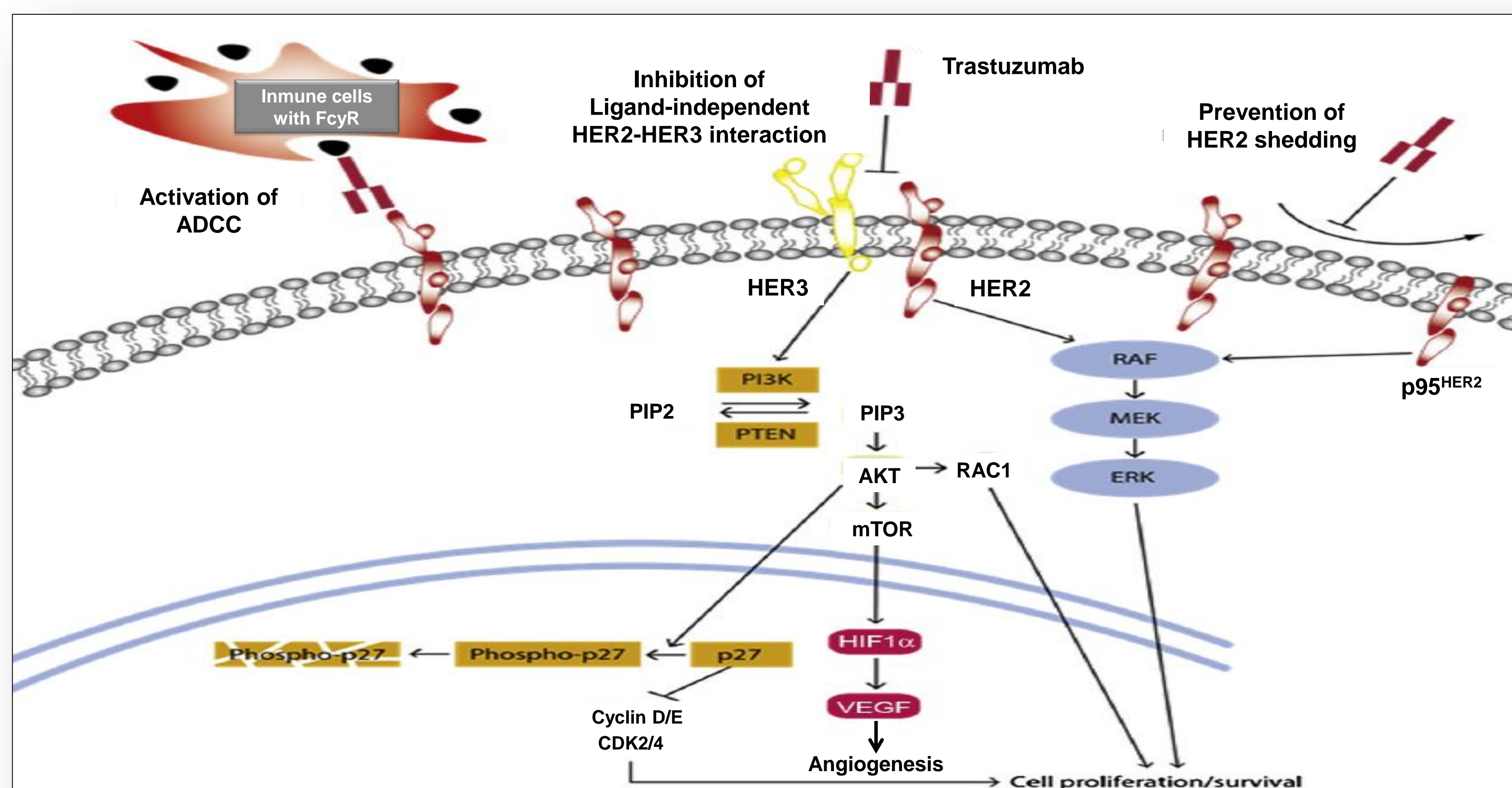


Figure 1. Mechanisms of Trastuzumab Action

- ❖ Effect on Cell Cycle
- ❖ Effect on the PI3K Pathway
- ❖ Inhibition of HER2 Extracellular Domain Proteolysis
- ❖ Inhibition of Angiogenesis
- ❖ Immune-Mediated Response

De, Pradip et al. *Cancer Treatment Reviews* , Volume 39 (2013) , 925 - 934

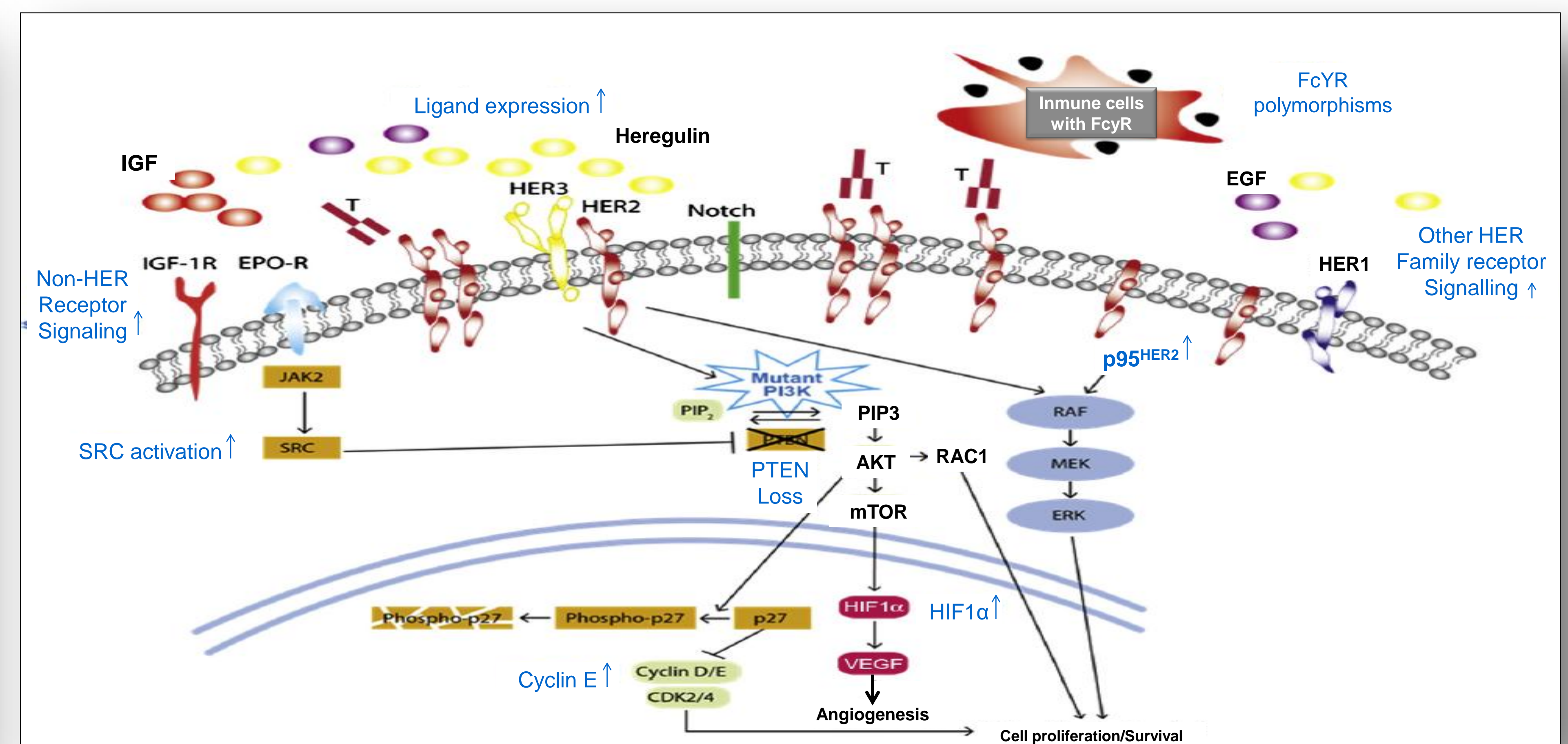


Figure 2. Main Mechanisms of Trastuzumab Resistance

- ❖ Truncated HER2 (p95HER2)
- ❖ Masking with MUC4
- ❖ PTEN Loss
- ❖ Increased PI3K/Akt Activity
- ❖ Modulation of p27^{Kip1}
- ❖ Insulin-Like Growth Factor-1 Receptor Overexpression
- ❖ Impaired Immune-Mediated Mechanisms
- ❖ Ligand-Induced HER2/HER3 Dimerization

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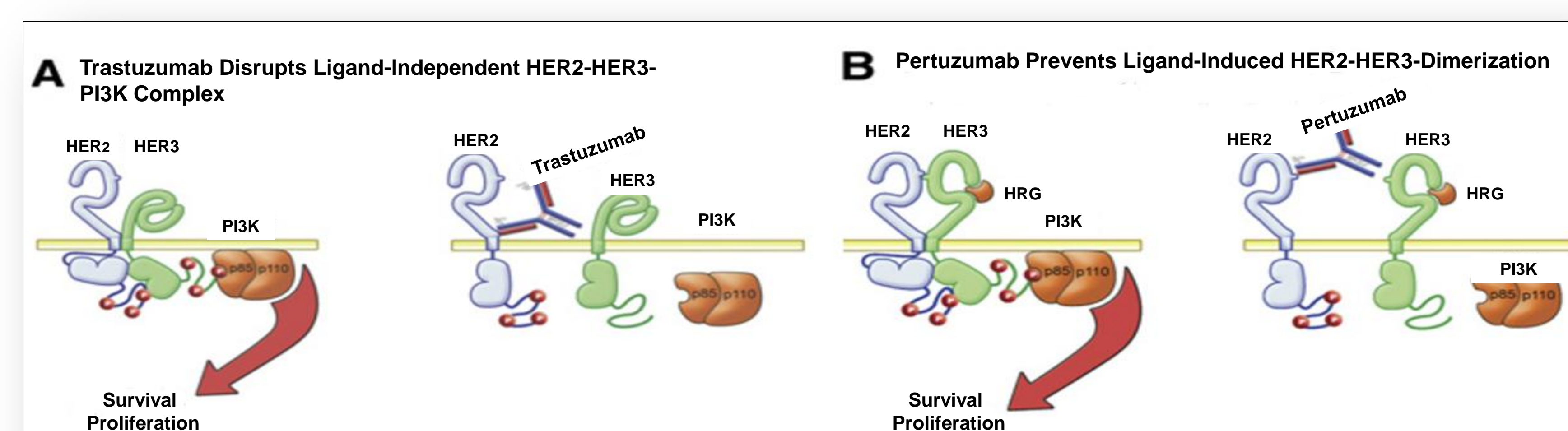


Figure 3. Mechanism of Action of Trastuzumab and Pertuzumab

- ❖ **Trastuzumab(A)** disrupts the ligand-independent HER2/HER3 dimerization , leading to rapid HER3 dephosphorylation and inhibition of the PI3K/AKT pathway, thereby inhibiting cell proliferation.
- ❖ **Pertuzumab(B)** disrupts the ligand-induced HER2/HER3 dimerization. Ligand-induced HER2/HER3 dimerization can occur in both HER2-amplified and nonamplified cells.

Edited from: Teemu T. Junttila et al. *Cancer Cell* 15, 429–440 (2009)

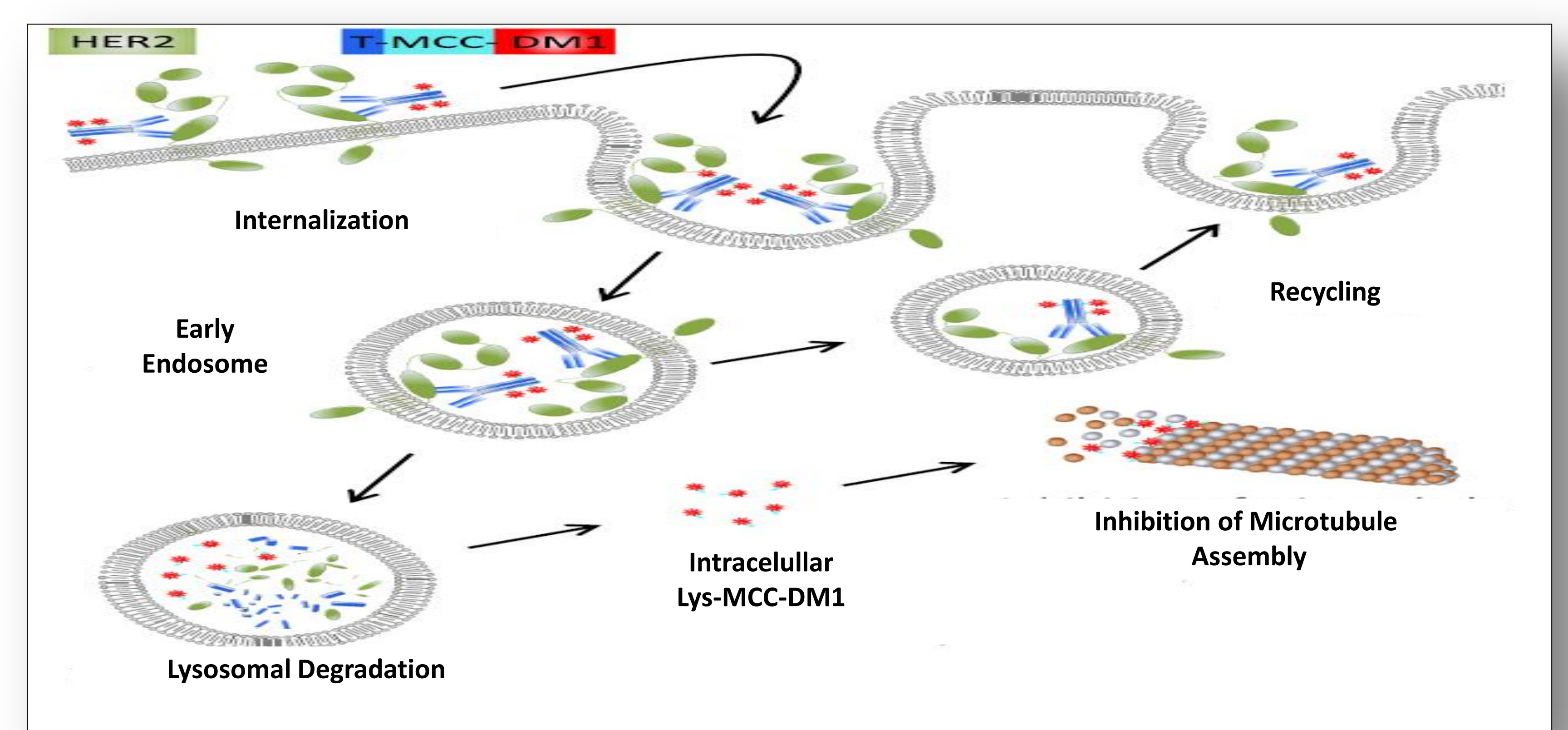


Figure 4. Main Mechanisms of T-DM1 Action

T-DM1 has mechanisms of action consisting of the anti-tumor effects related to Trastuzumab (discussed above) and those associated with intracellular DM1 metabolites, which are:

1. Inhibition of Microtubule Assembly
2. Mitotic Arrest
3. Disrupted Intracellular Trafficking
4. Mitotic Catastrophe
5. Apoptosis

Del Mastro, Lambertini, Bighin et al. *Expert Rev. Anticancer Ther.* 12(11), 1391–1405 (2012)

Conclusions

In recent years, the outcome for patients with HER2-positive breast cancer has improved markedly. Clinical guidelines recommend HER2-directed therapies as the backbone therapy for these patients. Nevertheless, resistance to HER2-directed therapies remains a challenge.

Clinical and basic research, suggest that combinations of HER2-directed agents may show additive or synergistic effects and lead to an improved outcome. However, apart from the overexpression of the HER2 protein and gene amplification, there isn't any other type of biomarker able to predict the response to current and future target therapies. Therefore, it is primordial to have a detailed knowledge about resistance mechanisms to approved and future drugs, in order to establish new biomarkers capable of predicting which drug or combinations would be the best in each case.